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(54) Title: USE OF 1,5-BENZODIAZEPINE DERIVATIVES FOR THE CONTROL OF GASTRIC EMPTYING IN PATIENTS WITH NON-INSULIN DEPENDENT DIABETES MELLITUS			
(57) Abstract			
The use of a compound of formula (1) or a physiologically salt thereof in the manufacture of a therapeutic agent for the treatment of early non-insulin dependent diabetic conditions.			

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USE OF 1,5-BENZODIAZEPINE DERIVATIVES FOR THE CONTROL OF GASTRIC
EMPTYING IN PATENTS WITH NON-INSULIN DEPENDENT DIABETES MELLITUS

This invention relates to a new medical use of 1,5-benzodiazepine derivatives which exhibit CCK-A agonist activity. More particularly it relates to the use of such compounds to control gastric emptying in patients having an early non-insulin-dependent diabetic condition.

Cholecystokinins (CCK) and gastrin are structurally related peptides which exist in gastrointestinal tissue and in the central nervous system. Cholecystokinins include CCK-33, a neuropeptide of thirty-three amino acids in its originally isolated form, its carboxyl terminal octapeptide, CCK-8 (also a naturally occurring neuropeptide), and 39- and 12-amino acid forms. Gastrin occurs in 34-, 17- and 14- amino acid forms, with the minimum active sequence being the C-terminal tetrapeptide, Trp-Met-Asp-Phe-NH₂ (CCK-4) which is the common structural element shared by both CCK and gastrin.

CCK and gastrin are gastrointestinal hormones and neurotransmitters in the neural and peripheral systems and perform their respective biological roles by binding to particular receptors located at various sites throughout the body. There are at least two subtypes of cholecystokinin receptors termed CCK-A and CCK-B and both are found in the periphery and in the central nervous system.

The CCK-A receptor, commonly referred to as the "peripheral-type" receptor, is primarily found in the pancreas, gallbladder, ileum, pyloric sphincter and on vagal afferent nerve fibers. Type-A CCK receptors are also found in the brain in discrete regions and serve to provide a number of CNS effects. Due to the ability of CCK-8 and Type-A CCK-selective agonists to suppress food intake in several animal species, considerable interest has been generated toward the development of new substances which function as Type-A receptor-selective CCK agonists in order to serve as anorectic agents.

The CCK-B or gastrin receptors are found in peripheral neurons, gastrointestinal smooth muscle and gastrointestinal mucosa, most notably in parietal cells, ECL cells, D cells and chief cells. CCK-B receptors also predominate in the brain and have been implicated in the regulation of anxiety, arousal and the action of neuroleptic agents.

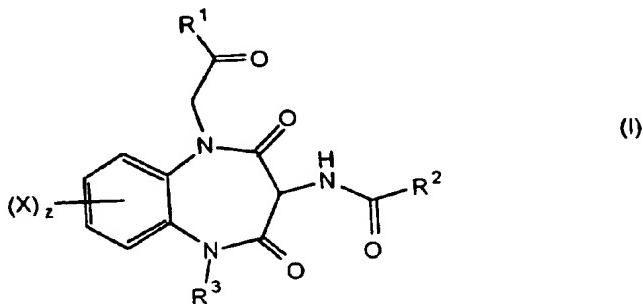
U.S. Patent No. 4,988,692, to Gasc, et al. describes a group of 3-acylamino 1-alkyl-5-phenyl 1,5-benzodiazepine derivatives which behave as cholecystokinin antagonists to reverse or block the effects of the endogenous hormone at its receptors.

5 US Patent No. 4,490,304 and PTC applications No's WO90/06937 and WO91/19733 describe peptide derivatives that exhibit CCK-A agonist activity. Such compounds have been disclosed for appetite regulation as well as the treatment and/or prevention of gastrointestinal disorders or disorders of the central nervous in animals and, more particularly, humans.

10 US Patent No. 5,187,154 which is incorporated herein by reference describes the use of the neuropeptide cholecystokinin (CCK) to control gastric emptying in patients having an early non-insulin-dependent diabetic condition and exhibiting rapid gastric emptying. Further the specification teaches that compounds which inhibit gastric emptying may be useful to alleviate or eliminate symptoms associated with early or pre-diabetes. Particular symptoms include elevated blood glucose and insulin levels, insulin resistance, increased susceptibility to infection or glycosuria while also maintaining gastric emptying within normal levels.

15 20 We have now discovered that a novel group of 3-amino 1,5-benzodiazepine compounds which exhibit agonist activity for the CCK-A receptor delay or inhibit gastric emptying and thus may be used to treat patients having non-insulin-dependent diabetic conditions and exhibiting rapid gastric emptying.

25 The present invention thus provides for the use of compounds of the general Formula (I)

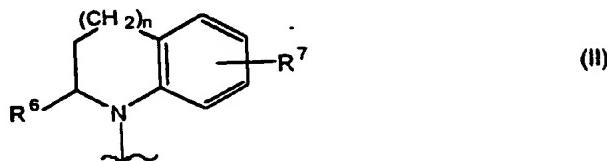


and physiologically salts and solvate thereof wherein:

X is either hydrogen, trifluoromethyl, alkyl, C₁₋₄alkylthio, -O(C₁₋₄alkyl) or halogen;

5

R¹ is either Formula II or -NR⁴R⁵;



10 R² is either:

(1) a heterocycle linked at its 2- position and selected from pyrrole, tetrahydropyrrrole, indole, benzofuran, thiophene, benzothiophene, indoline,

15 quinoline or 4-oxobenzopyran and wherein said pyrrole, tetrahydropyrrole, indole or indoline may optionally be substituted on the ring nitrogen thereof by the group R⁸ as defined hereunder and said indole, indoline, quinaline, benzofuran, benzothiophene or 4-oxo-benzopyran may optionally be substituted in the benzo ring thereof by the group R⁹ as defined hereunder or

20

(2) phenyl or phenyl mono- or disubstituted independently with halogen, hydroxy, cyano, carboxy, -O(C₁₋₄alkyl), -O(CH₂C₆H₅), -COO(C₁₋₄alkyl), amino, dimethylamino, -NHR¹⁰, 1-pyrrolidinyl or tetrazolyl; or

25

(3) pyridine or pyridinyl mono- or disubstituted independently with halogen, methyl, hydroxy, nitro, cyano, carboxy, -O(C₁₋₄ alkyl), -O(CH₂C₆H₅), -COO(C₁₋₄alkyl), amino or dimethylamino; or

30 (4) -NHR¹¹ where R¹¹ is defined hereinunder or R¹¹ is 7-indazolyl containing a group R¹⁰ at the N-1 position;

R₃ is hydrogen, C₁-6alkyl, C₃-cycloalkyl, phenyl or phenyl mono- or disubstituted independently with halogen;

5 R₄ is independently C₃-6alkyl, C₃-cycloalkyl, C₃-6alkenyl, phenyl, -(CH₂)_pCN or -(CH₂)_pCOO(C₁-4alkyl) and R₅ is independently C₃-6alkyl, C₃-cycloalkyl, C₃-6alkenyl, benzyl, phenyl or phenyl mono- or disubstituted independently with C₁-3alkyl, optionally substituted by 1 or more fluorine atoms cyano, hydroxy, 10 dimethylamino, -O(C₁-4alkyl), -O(CH₂C₆H₅), -NH(C₁-4alkyl), -COO(C₁-4alkyl), N(C₁-4alkyl)₂ pyrrolidino, morpholino or halogen or R₄ is C₁-2alkyl and R₅ is phenyl substituted at the 2- or 4- position with chloro, methyl, methoxy or methoxycarbonyl;

R₆ is hydrogen or methyl;

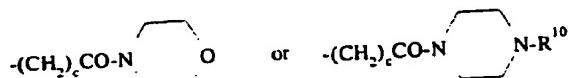
15 R₇ is hydrogen, hydroxy, fluoro, dimethylamino, -O(C₁-4alkyl) or -O(CH₂C₆H₅);

R₈ is -(CH₂)_bCOOH;

20 R₉ is methyl, chloro, nitro, hydroxy, methoxy or -NHR¹⁰;
R₁₀ is hydrogen, acetyl, C₁-4alkyl, -SO₃H, -SO₂CH₃, -SO₂CF₃ or -SO₂C₆H₅.

25 R₁₁ is phenyl or phenyl mono- or disubstituted independently with fluorine, trifluoromethoxy, C₁-4alkylthio, -(CH₂)_cCOOH, -(CH₂)_cCOO(C₁-4alkyl), -(CH₂)_cSCH₃, -(CH₂)_cSOCH₃, -(CH₂)_cSO₂CH₃, -(CH₂)_cCONH₂, -SCH₂COOH, -CONH(SO₂CH₃), -(CH₂)_cN(C₁-4alkyl)₂, -(CH₂)_cN(SO₂CF₃)(C₁-4alkyl), -(CH₂)_cSO₂NHCO(C₁-4alkyl), -(CH₂)_cSO₂N(C₁-4alkyl), -(CH₂)_cCON(C₁-4alkyl)CO(C₁-4alkyl), -(CH₂)_cCONHSO₂(C₁-4alkyl), -(CH₂)_cCON(C₁-4alkyl)SO₂(C₁-4alkyl), -(CH₂)_cOR¹², -(CH₂)_cNHR¹⁰ or phenyl monosubstituted with -(CH₂)_c(tetrazolyl), -(CH₂)_c(carboxamidotetrazolyl) or -(CH₂)_c(pyrrolidinyl) or R₁₁ is selected from pyridine or pyridinyl mono- or disubstituted independently with halogen, methyl, hydroxy, nitro, cyano, carboxy, -O(C₁-4 alkyl), amino, dimethylamino, -NHR¹⁰;

R₁₂ is hydrogen, C₁₋₆alkyl, C₃₋₆cycloalkyl, -CH₂C₆H₅, -CH₂COOH,
-CH₂CONH₂, -CH₂CONH(C₁₋₄alkyl), -CH₂CON(C₁₋₄alkyl)₂ or



5 z is 1 or 2;

n is 1 or 2;

p is an integer from 1-4;

10 b is an integer from 0-3; and

c is 0 or 1,

15 in the manufacture of a therapeutic agent for controlling gastric emptying in patients having an early non-insulin-dependent diabetic condition and exhibiting rapid gastric emptying.

20 When R¹ represents the group of Formula (II), examples of such a group include those wherein R⁶ is hydrogen or more particularly methyl, R⁷ is hydrogen, hydroxyl, methoxy, or fluorine, and n is 1.

25 When R¹ represents the group NR⁴R⁵, examples of suitable groups include those wherein R⁴ represent C₃₋₆ alkyl, such as propyl or isopropyl, cyclohexyl or phenyl and R⁵ represents C₃₋₆ alkyl, benzyl or phenyl optionally substituted in the para- position by hydroxy, dimethylamino methoxy, trifluoromethyl, fluorine, pyrrolidino or morpholino. Within this group, particularly useful R¹ groups include those wherein R⁴ is propyl and, more particularly, isopropyl and R⁵ represents phenyl or phenyl substituted in the para-position by groups selected from hydroxy, methoxy dimethylamino, fluorine, or morpholino.

30 Examples of particularly suitable R¹ groups include those wherein R¹ is the group of Formula (II) wherein R⁶ is methyl, n is 1 and R⁷ is hydrogen, hydroxy, fluorine or methoxy or R¹ is the group NR⁴R⁵ wherein R⁴ is propyl or isopropyl and R⁵ is

phenyl optionally substituted in the para position by a group selected from phenyl optionally substituted in the para position by a group selected from hydroxy, methoxy, fluoro, trifluoromethyl, dimethylamino, pyrrolidino or morpholino.

5 When R² represents a group selected from indole, indoline, benzofuran, benzothiophene, quinoline or 4-oxobenzopyran, the optional substituent R⁹ is conveniently a group selected from hydrogen, methyl, methoxy, hydroxy, nitro or amino and, where appropriate, the optional substituent on nitrogen, (R⁸), is -CH₂CO₂H.

10 When R² is an optionally substituted phenyl group, this is conveniently phenyl or phenyl substituted by one or two groups, which may be the same or different and selected from chlorine, fluorine, amino, hydroxy or carboxyl.

15 When R² represents the group NHR¹¹, R¹¹ is conveniently phenyl (optionally substituted by fluoro, hydroxy, amino, dimethylamino, trifluoromethylsulphonylamino, C₁₋₄ alkoxy carbonyl, carboxy, 1H-tetrazol-5-yl, acetyl amino or OR¹² wherein R¹² represents hydrogen, methyl, benzyl, CH₂CO₂H, CH₂CONH₂, CH₂CONHCH₃, CH₂CON(CH₃)₂



) or a 7-indazolyl group wherein the N-1 substituent, (R¹⁰), is hydrogen.

When R¹¹ is a mono substituted phenyl group, the substituted is conveniently in the meta- position.

25 Examples of particularly suitable R² groups includes indole, benzofuran, thiophene, benzothiophene, indoline, quinoline, 4-oxobenzopyran, an optionally substituted phenyl group or the group NHR¹¹. Conveniently, R² is selected from the group indole, indoline or benzofuran, an optionally substituted phenyl group or the group NHR¹¹. More particularly, R² represents an indole, an optionally substituted phenyl or NHR¹¹.

30 When R₃ represents C₁₋₆ alkyl, examples of suitable groups include methyl, ethyl, propyl, isopropyl, butyl, t-butyl or isoamyl.

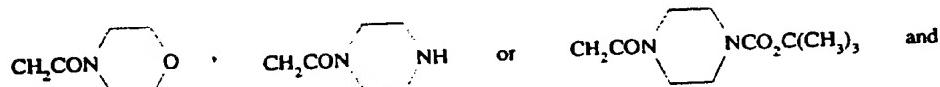
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When R₃ represents C₃₋₆ cycloalkyl, examples of suitable groups include cyclopropyl, cyclopentyl or cyclohexyl.

- 5 When R₃ represents phenyl, mono or disubstituted by independently with halogen, examples of suitable groups include those wherein the halogen substituent is fluorine e.g., 2-fluorophenyl or 4-fluorophenyl.

- 10 Examples of particularly suitable R³ groups include hydrogen, methyl, cyclohexyl, 2-fluorophenyl or phenyl, and more particularly, phenyl.

- A particularly useful group of compounds for use according to the invention include those wherein R¹ represents the group of Formula (II) wherein R⁶ is methyl, n is 1 and R⁷ is hydrogen, fluorine, hydroxy or methoxy, or more particularly NR⁴R⁵ wherein R⁴ is propyl or isopropyl and R⁵ is phenyl optionally substituted in the para position by a group selected from hydroxy, methoxy, fluoro, dimethylamino or monopholino; R² represents phenyl (optionally substituted independently by one or two groups selected from chlorine, fluorine, hydroxy, amine or carboxy), NHR¹¹ wherein R¹¹ represents phenyl (optionally substituted amino or carboxy), CH₂CONH¹² wherein R¹² represents hydrogen, methyl, benzyl, acetyl or OR¹² where R¹² represents hydrogen, methyl, benzyl, CH₂CO₂H, CH₂CONH₂, CH₂CONHCH₃, CH₂CON(CH₃)₂.



- 25 wherein the substituent is preferably in the meta- position) or an indole wherein the nitrogen atom is optionally substituted by the group -CH₂CO₂H and the benzene ring is optionally substituted by chlorine, methyl, methoxy, nitro, hydroxy or amino; R³ represents hydrogen, methyl, cyclohexyl, 2- fluorophenyl or phenyl or, more particularly, 2 fluorophenyl or phenyl; and X represents fluorine and z is 1 or, more particularly, X is hydrogen;

- 30 A particularly interesting class of compounds for use in the present invention are those wherein R² is an indole group. A preferred group of compounds within this class are those wherein the indole group is substituted on the nitrogen atom by the group -CH₂CO₂H or, more preferably, the nitrogen atom is unsubstituted,

and benzo ring of the indole group is optionally substituted by a group selected from chlorine, methyl, methoxy, nitro, hydroxy or amino.

- A particularly preferred compound for use in the invention which is hereinafter referred to as compound 'A' is:
- 5 1H-Indole-2-carboxylic acid {1-[Isopropyl-(4-methoxyphenyl)carbamoyl-methyl]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl}-amide and enantiomers thereof.

- 10 As provided herein, the term alkyl is generally intended to mean both straight chain and branched chain aliphatic isomers of the corresponding alkyl. For example, C₁-6alkyl is intended to include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tertbutyl, n-pentyl, etc.

- 15 The term cycloalkyl, as provided herein, is intended to mean all alicyclic isomers of the corresponding alkyl. For example, the term C₃-6 alkyl, as provided herein, is intended to include such groups as cyclopropyl, cyclopentyl and cyclohexyl.

- The term halogen is intended to mean F, Cl, Br or I.
- 20 The term tetrazole as a group or part of a group refers to the (1 H)-tetrazol-5-yl grouping and tautomers thereof.

- 25 Those skilled in the art will recognize that stereocenters exist in compounds of Formula (I). Accordingly, the present invention includes all possible stereoisomers and geometric isomers of Formula (I) and includes not only racemic compounds but also the optically active isomers as well. When a compound of Formula (I) is desired as a single enantiomer, it may be obtained either by resolution of the final product or by stereospecific synthesis from either isomerically pure starting material or any convenient intermediate. Resolution of the final product, an intermediate or a starting material may be effected by any suitable method known in the art. See, for example, Stereochemistry of Carbon Compounds by E. L. Eliel (Mcgraw Hill, 1962) and Tables of Resolving Agents by S. H. Wilen. Additionally, in situations where tautomers of the compounds of Formula (I) are possible, the present invention is intended to include all tautomeric forms of the compounds.
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It will also be appreciated by those skilled in the art that the compounds of the present invention may also be utilized in the form of a pharmaceutically acceptable salt or solvate thereof. The physiologically acceptable salts of the compounds of Formula (I) include conventional salts formed from 5 pharmaceutically acceptable inorganic or organic acids as well as quaternary ammonium acid addition salts. More specific examples of suitable salts include hydrochloric, hydrobromic, sulphuric, phosphoric, nitric, perchloric, fumaric, acetic, propionic, succinic, glycolic, formic, lactic, maleic, tartaric, citric, pamoic, malonic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, fumaric, toluenesulphonic, methanesulphonic, naphthalene-2-sulphonic, benzenesulphonic 10 and the like. Other acids such as oxalic, while not in themselves pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable salts. References hereinafter to a compound according to the invention include 15 both compounds of Formula (I) and their pharmaceutically acceptable salts and solvates.

20 CCK-A agonist activity of the compounds of formula (I) may be determined by standard procedures.

25 The relative affinities of compounds of formula (I) for the CCK-A and CCK-B receptors may also be determined using known conventional procedures such as described by Fornos et al J. Pharmacol Exp. Ther., 1992 261, 1056-1063.

30 The compounds of formula (I) inhibit or delay gastric emptying and thus may be used to alleviate or eliminate symptoms associated with early or prediabetes, particularly for non-insulin dependent diabetes. Such symptoms include elevated blood glucose and insulin levels, insulin resistance, increased susceptibility to infection and/or glycosuria while also maintaining gastric emptying with normal levels.

35 The ability of compounds of formula (I) to inhibit or delay gastric emptying may be determined using standard tests. Thus for example rats deprived for food for 18hr were pretreated with the test compound administered i.p at a pre-set time (20 mins) before being given a methyl cellulose meal which was administered by the gavage route. The meal contains a marker element such as Phenol Red. After

specific predetermined time intervals the rats are sacrificed and the amount of the meal in the stomach is determined by measuring the concentration of the marker substance present. This value is then compared with a control animal which was not pre-treated with the test compound. In this test the preferred compound of formula (I) compound 'A' when administered i.p at doses of 1 μ mole/kg 20 min before gavage of test meal (1.5% methyl cellulose), completely inhibited gastric emptying 30mins after administration of the test meal. Lower doses of the compound 'A' 0.01 and 0.1 μ moles per kg i.p also resulted in a significant reduction in gastric emptying.

According to a further aspect of the present invention, there is provided herein a method for the treatment of a mammal, including man, in particular in the treatment associated with early or prediabetes, particularly noninsulin-dependent diabetes, the method comprising administering to the patient exhibiting rapid gastric emptying an therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt or solvate thereof.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established diseases or symptoms. Moreover, it will be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. In general, however, doses employed for adult human treatment will typically be in the range of 0.02 - 5000 mg per day, e.g., 1-1500 mg per day. The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

While it is possible that compounds of formula (I) may be therapeutically administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceutical formulation. Accordingly, the present invention further provides for a pharmaceutical formulation for use in the present invention comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof together with one or more pharmaceutically acceptable carriers therefore and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s)

must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

- Formulations of the present invention include those especially formulated for oral, buccal, parenteral, implant, or rectal administration, however, oral administration is preferred. For buccal administration, the composition may take the form of tablets or lozenges formulated in conventional manner. Tablets and capsules for oral administration may contain conventional excipients such as binding agents, (for example, syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinylpyrrolidone), fillers (for example, lactose, sugar, microcrystalline cellulose, maize-starch, calcium phosphate or sorbitol), lubricants (for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica), disintegrants (for example, potato starch or sodium starch glycollate) or wetting agents, such as sodium lauryl sulphate. The tablets may be coated according to methods well-known in the art. Such tablet coatings conveniently include conventional enteric coatings known to those skilled in the art e.g. cellulose acetate phthalate, polyvinyl acetate phthalate, shellac, styrene maleic acid copolymers, methyacrylic acid copolymers and hydroxypropyl methyl cellulose phthalate.
- Alternatively, the compounds of the present invention may be incorporated into oral liquid preparations such as aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, for example. Moreover, formulations containing these compounds may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents such as sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminum stearate gel or hydrogenated edible fats; emulsifying agents such as lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils) such as almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; and preservatives such as methyl or propyl p-hydroxybenzoates or sorbic acid. Such preparations may also be formulated as suppositories, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.
- For oral administration the compounds of formula (I) are preferably formulated as enteric coated tablets or enteric capsules.

Pharmacy**Tablet**

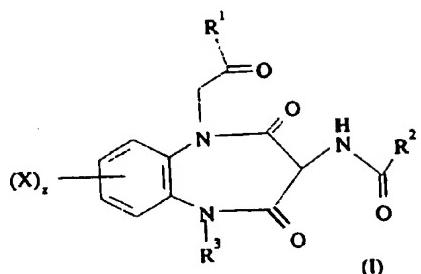
5	Active Ingredient	50 mg
	Lactose anhydrous USP	163 mg
	Microcrystalline Cellulose NF	69 mg
	Pregelatinized starch Ph. Eur.	15 mg
	Magnesium stearate USP	3 mg
10	Compression weight	300 mg

The active ingredient, microcrystalline cellulose, lactose and pregelatinized starch are sieved through a 500 micron sieve and blended in a suitable mixer. The
15 magnesium starate is sieved through a 250 micron sieve and blended with the active blend. The blend is compressed into tablets using suitable punches, then coated in a conventional manner with an enteric coating such as cellulose acetate phthalate.

Claims

1. The use of a compound of Formula (1)

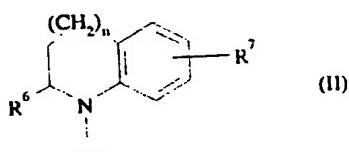
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and physiologically salts and solvate thereof wherein:

10 X is either hydrogen, trifluoromethyl, alkyl, C1-4alkylthio, -O(C1-4alkyl) or halogen;

R¹ is either Formula II or -NR⁴R⁵:



15

R² is either:

(1) a heterocycle linked at its 2- position and selected from pyrrole, tetrahydropyrrole, indole, benzofuran, thiophene, benzothiophene, indoline, quinoline or 4-oxobenzopyran and wherein said pyrrole, tetrahydropyrrole, indole or indoline may optionally be substituted on the ring nitrogen thereof by the group R⁸ as defined hereunder and said indole, indoline, quinoline, benzofuran, benzothiophene or 4-oxo-benzopyran may optionally be substituted in the benzo ring thereof by the group R⁹ as defined hereunder or

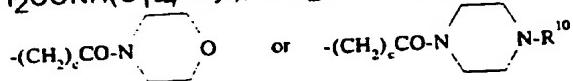
- (2) phenyl or phenyl mono- or disubstituted independently with halogen, hydroxy, cyano, carboxy, -O(C₁₋₄alkyl), -O(CH₂C₆H₅), -COO(C₁₋₄alkyl), amino, dimethylamino, -NHR¹⁰, 1-pyrrolidinyl or tetrazolyl; or
- 5 (3) pyridine or pyridinyl mono- or disubstituted independently with halogen, methyl, hydroxy, nitro, cyano, carboxy, -O(C₁₋₄ alkyl), -O(CH₂C₆H₅), -COO(C₁₋₄alkyl), amino or dimethylamino; or
- 10 (4) -NHR¹¹ where R¹¹ is defined hereinunder or R¹¹ is 7-indazolyl containing a group R¹⁰ at the N-1 position;
- R³ is hydrogen, C₁₋₆alkyl, C₃₋₆cycloalkyl, phenyl or phenyl mono- or disubstituted independently with halogen;
- 15 R⁴ is independently C₃₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆alkenyl, phenyl, -(CH₂)_pCN or -(CH₂)_pCOO(C₁₋₄alkyl) and R⁵ is independently C₃₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆ alkenyl, benzyl, phenyl or phenyl mono- or disubstituted independently with C₁₋₃alkyl, cyano, hydroxy, dimethylamino, -O(C₁₋₄alkyl), -O(CH₂C₆H₅), -NH(C₁₋₄alkyl), -COO(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂ pyrrolidino, morpholino or R⁴ is C₁₋₂alkyl and R⁵ is phenyl substituted at the 2- or 4- position halogen or R⁴ is C₁₋₂alkyl and R⁵ is phenyl substituted at the 2- or 4- position with chloro, methyl, methoxy or methoxycarbonyl;
- R⁶ is hydrogen or methyl;
- 25 R⁷ is hydrogen, hydroxy, fluoro, dimethylamino, -O(C₁₋₄alkyl) or -O(CH₂C₆H₅);
- R⁸ is -(CH₂)_bCOOH;
- R⁹ is methyl, chloro, nitro, hydroxy, methoxy or -NHR¹⁰;
- 30 R¹⁰ is hydrogen, acetyl, C₁₋₄alkyl, -SO₃H, -SO₂CH₃, -SO₂CF₃ or -SO₂C₆H₅, C₁₋₄alkoxycarbonyl;
- 35 R¹¹ is phenyl or phenyl mono- or disubstituted independently with fluorine, trifluoromethoxy, C₁₋₄alkylthio, -(CH₂)_cCOOH, -(CH₂)_cCOO(C₁₋₄alkyl), -(CH₂)_cSCH₃, -(CH₂)_cSOCH₃, -(CH₂)_cSO₂CH₃, -(CH₂)_cCONH₂, -SCH₂COOH, -CONH(SO₂CH₃), -CONH(SO₂CF₃), -(CH₂)_cN(C₁₋₄alkyl)₂, -(CH₂)_cNH(SO₂CF₃), -(CH₂)_cN(SO₂CF₃)(C₁₋₄alkyl), -(CH₂)_cSO₂NHCO(C₁₋₄alkyl).

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15

4alkyl), -(CH₂)_cSO₂N(C₁-4alkyl)CO(C₁-4alkyl), -(CH₂)_cCONHSO₂(C₁-4alkyl), -(CH₂)_cCON(C₁-4alkyl)SO₂(C₁-4alkyl), -(CH₂)_cOR¹² -(CH₂)_cNHR¹⁰ or phenyl monosubstituted with -(CH₂)_c(tetrazolyl), -(CH₂)_c (carboxamidotetrazolyl) or -(CH₂)_c(pyrrolidinyl) or R¹¹ is selected from pyridine or pyridinyl mono- or disubstituted independently with halogen, methyl, hydroxy, nitro, cyano, carboxy, -O(C₁-4 alkyl), amino, dimethylamino, -NHR¹⁰;

5 R¹² is hydrogen, C₁-6alkyl, C₃-6cycloalkyl, -CH₂C₆H₅, -CH₂COOH, -CH₂CONH₂, -CH₂CONH(C₁-4alkyl), -CH₂CON(C₁-4alkyl)₂ or



10

z is 1 or 2;

n is 1 or 2;

15 p is an integer from 1-4;

b is an integer from 0-3; and

c is 0 or 1.

20

in the manufacture of a therapeutic agent for controlling gastric emptying in patients having an early non-insulin-dependent diabetic condition and exhibiting rapid gastric emptying.

25

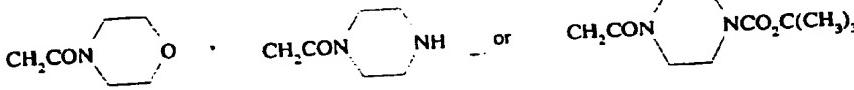
2. The use of a compound as claimed in Claim 1 wherein R¹ represents the group of Formula (II) wherein R⁶ is methyl, R⁷ is hydrogen, hydroxyl, methoxy or fluorine and n is 1 or R¹ represents the group NR⁴R⁵ wherein R⁴ represents C₃-6 alkyl, cyclohexyl or phenyl, and R⁵ represents C₃-6 alkyl or phenyl optionally substituted in the para position by hydroxy, dimethylamino, methoxy, fluorine, pyrrolidino or morpholino.

30

3. The use of a compound as claimed in Claims 1 or 2 wherein R¹ represents the group NR⁴R⁵ and R⁴ represents propyl or isopropyl and R⁵ represents phenyl or phenyl substituted in the para position by a group selected from hydroxy, methoxy, dimethylamino, fluorine, or morpholino.

35

4. The use of a compound as claimed in any of Claims 1 to 3 wherein R² represents a group selected from phenyl (optionally substituted by one or two groups which may be the same or different and selected from chlorine, fluorine, amino, hydroxy or carboxy,) or NHR¹¹ wherein R¹¹ is phenyl (optionally substituted by fluoro, hydroxy, amino, dimethylamino, trifluoromethylsulphonylamino, C₁₋₄ alkoxycarbonyl, carboxy, 1H-tetrazol-5-yl, acetylamino or OR¹² wherein R¹² represents hydrogen, methyl, benzyl, CH₂CO₂H, CH₂CONH₂, CH₂CONHCH₃, CH₂CON(CH₃)₂

5 

10) or 7-indazolyl wherein the N-1 substituted is hydrogen, or R² represents an indole group wherein the nitrogen atom is optionally substituted by the group -CH₂CO₂H and the benzo ring is optionally substituted by a group selected from chlorine, methyl, methoxy, nitro, hydroxy or amino.

15 5. The use of a compound as claimed in any of Claims 1-4 wherein R² represents an indole group which is unsubstituted on the nitrogen atom and in which the benzo ring thereof is optionally substituted by a group selected from chlorine, methyl, methoxy, nitro, hydroxy or amino.

20 6. The use of a compound as claimed in any of Claims 1-5 wherein R³ represents hydrogen, methyl, cyclohexyl, 2-fluorophenyl or phenyl.

25 7. The use of a compound as claimed in any of Claims 1-6 wherein R³ represents phenyl.

30 8. The use of a compound as claimed in any of Claims 1-7 wherein X represents hydrogen.

35 9. The use of a compound as claimed in Claim 1 wherein R¹ represents NR⁴R⁵ and R⁴ represents isopropyl and R⁵ represents p-methoxyphenyl; R² represents an unsubstituted 2-indole group; R³ represents phenyl and X represents hydrogen and enantiomers thereof.

40 10. A method for the treatment of early or pre-non-insulin dependant diabetes which comprises administering to the patient exhibiting rapid gastric

emptying a therapeutically effective amount of a compound of formula (1) or a physiologically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 95/12830

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO,A,94 24149 (GLAXO INC ; SUGG ELIZABETH ELLEN (US); AQUINO CHRISTOPHER JOSEPH (U) 27 October 1994 see the whole document especially page 9, line 4-11 ---	1-10
A	US,A,5 187 154 (PHILLIPS WILLIAM ET AL) 16 February 1993 cited in the application see the whole document ---	1-10 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *'A' document defining the general state of the art which is not considered to be of particular relevance
- *'E' earlier document but published on or after the international filing date
- *'L' document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *'O' document referring to an oral disclosure, use, exhibition or other means
- *'P' document published prior to the international filing date but later than the priority date claimed

- *'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *'Z' document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

20.02.96

6 February 1996

Authorized officer

Mair, J

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 95/12830

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category	Citation of document, with indication, where appropriate, of the relevant passages
A	SCAND J GASTROENTEROL, MAY 1993, 28 (5) P401-7, NORWAY, KONTUREK JW ET AL 'Cholecystokinin in the regulation of gastric acid and endocrine pancreatic secretion in humans.' see the whole document especially page 405, left column, line 11-page 406, right column, line 19 -----
A	J PHYSIOL PARIS, 1993, 87 (5) P291-300, FRANCE, SCARPIGNATO C ET AL 'Effect of CCK and its antagonists on gastric emptying.' see the whole document especially page 297, left column, line 11-17 -----

INTERNATIONAL SEARCH REPORT

I national application No.

PCT/US 95/ 12830

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although Claim 10 is directed towards a method of treatment of the

human or animal body the search has been carried out and based on the
alleged effects of the compounds.

2. Claims Nos.: all claims because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
In view of the large number of compounds which are theoretically defined by the formula of claim 1, the search has to be restricted on economic grounds to the preferred compounds and the general concept of the application.

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 95/12830

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9424149	27-10-94	AU-B- 6567594	08-11-94
		AU-B- 6567694	08-11-94
		CA-A- 2158972	27-10-94
		CA-A- 2158973	27-10-94
		WO-A- 9424151	27-10-94
		EP-A- 0694040	31-01-96
		EP-A- 0694039	31-01-96
		FI-A- 954852	12-10-95
		FI-A- 954853	12-10-95
		NO-A- 954090	13-12-95
		NO-A- 954091	13-12-95
US-A-5187154	16-02-93	US-A- 5468727	21-11-95